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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/509,418	07/11/00	KOROPATNICK D	PM 266291

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EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	5

DATE MAILED: 01/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/509,418	Applicant(s) KOROPATNICK ET AL.	
	Examiner Janet L Epps	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 July 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Sequence

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). A computer readable form (CRF) of the sequence listing was submitted. However, the CRF could not be processed by the Scientific and Technical Information Center (STIC) for the reason(s) set forth on the attached CRF Diskette Problem Report.

A complete response to this Office Action requires that applicant's comply with the sequence rules and provide an adequate response to all pending rejections in this action. A response that does not address all of these issues will be held nonresponsive. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply.

Specification

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Drawings

3. The drawings filed 7-11-2000 are approved by the Draftsperson under 37 CFR 1.84 or 1.152.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 recites "the combination product" in claim 4, there is lack of antecedent basis for this limitation in the claim.

Claim 10 recites" the combination product" in claim 4, there is lack of antecedent basis for this limitation in the claim.

Claim 10 provides for the use of the combination product of claim 4, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 10 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-2, and 5-7 are rejected under 102(b) as being anticipated by Demoor et al. (Abstract, p. 419)

Claims 1-2 read on an antisense oligonucleotide which hybridizes to a target nucleic acid sequence in thymidylate synthase.

Demoor et al. disclose a method of down regulating thymidylate synthase activity in human tumor cells by administration of antisense oligonucleotides to said cells. Demoor et al. also teach the combination of thymidylate synthase antisense oligonucleotide and chemo-therapeutic drugs such as Tomudex and 5-fluorouracil.

Demoore et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

8. Claims 1-6 are rejected under 35 USC 102(b) as being anticipated by Ju et al.

Claims 1-6 read on an antisense oligonucleotide which hybridizes to a target nucleic acid sequence in thymidylate synthase, claims 3-4 recite antisense oligonucleotides according to claims 1-2 "comprising" SEQ ID NO: 1-9.

Ju et al. teach that expression of an antisense vector comprising the antisense sequence of thymidylate synthase they were able to increase the chemo-sensitivity of cancer cells to fluoropyrimidine drugs (p. 128, lines 1-6). Although, Ju et al. does not disclose specific oligonucleotides comprising the sequence of SEQ ID NO: 1-9, due to the open language of these claims ("comprising" SEQ ID NO: 1-9), the antisense vector comprising the thymidylate synthase coding sequence comprises the sequence of SEQ ID NO: 1-9. Ju et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2, 5, 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims read on antisense oligonucleotide which hybridises to a target nucleic acid sequence in thymidylate synthase (TS). However, the claims embrace a genus of nucleic acid sequences that read on antisense oligonucleotides targeting a genus of nucleic acid molecules encoding TS comprising any polymorphic variant of TS, and homologues of TS isolated from any organism. However, the instant claims read on nucleic acid molecules encoding TS that are beyond the scope of the specification as filed.

The applicant does not disclose any other nucleotide structures corresponding to the TS gene besides that of the human TS sequence according to GenBank accession no X02308 (p. 15, line 19). The specification does not provide any common structural or functional attributes which would identify the members of the claimed genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed

genus, and because the genus is highly variant, the specification alone is not sufficient to describe claimed genus.

Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application.

9. Claims 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 8-10 read on pharmaceutical compositions comprising an antisense oligonucleotide targeted to thymidylate synthase in combination with an anticancer agent and methods for the treatment of cancer comprising the administration of a antisense oligonucleotides targeted to thymidylate synthase.

Applicants specification fails to provide sufficient guidance to the skilled artisan on the parameters for practicing a method of nucleic acid therapy in an individual *in vivo* comprising the administration of a complex comprising TS antisense oligonucleotides for the breadth of the claimed invention. Numerous factors complicate the nucleic acid based therapy, which have not been overcome by routine experimentation. These include, the controlling the fate of the nucleic acid itself once administered to an individual (volume of distribution, rate of clearance into the tissues, etc.), controlling the *in vivo* consequences of altered gene expression and protein function, the fraction of nucleic acid taken up by the target cell population, predicting the trafficking of the

genetic material within cellular organelles, the rate of degradation of the nucleic acid, and the stability of the nucleic acid within a cell.

It is well established in the art that there is a significant level of unpredictability regarding the behavior of nucleic acid base therapeutics. According to Crooke (1998), states that "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Furthermore, Crooke teaches that variations in cellular uptake and distribution of oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Crooke also states that protein binding in general by nucleic acid based therapeutics may influence cell uptake, distribution, metabolism and excretion of the oligonucleotide. Furthermore, such protein binding may produce effects that can be mistakenly interpreted as the result of the nucleic acid alone. In addition to proteins, nucleic acids may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins, will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of nucleic acid based compounds thereby rendering the activity and behavior of nucleic acid based therapeutics unpredictable, and thus much experimentation is required to screen multiple nucleic acid compounds to determine not only their efficacy *in vitro* but also *in vivo*.

Additionally, the specification does not provide any working examples that enable the claimed invention. Nor does the specification provide any guidance to the skilled

artisan on how to make and use the claimed TS antisense oligonucleotides, which would produce a desired effect, namely for use in treating a patient in need of therapy. Even assuming that an effective TS antisense oligonucleotide is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit.

The amount of experimentation necessary to practice the claimed invention would require providing a means to deliver the TS antisense oligonucleotides to the correct target tissues associated with said disease or condition in a sufficient amount and duration, so as to produce a desired therapeutic result. Such guidance is not provided in the specification as filed or in the prior art of record at the time of filing of the instant application. Furthermore, a development of this scale in the unpredictable nucleic acid therapy art would have been considered to necessitate undue experimentation on the part of the skilled practitioner.

Therefore, the specification as filed does not describe the use of TS antisense oligonucleotides in a method of nucleic acid therapy, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. This conclusion is based upon the known unpredictability regarding the behavior of nucleic acid based therapeutics *in vivo* and further with the production of the desired secondary effects, such as treating a patient in need of therapy, and the lack of guidance in the specification as filed in this regard.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps whose telephone number is 703-308-8883. The examiner can normally be reached on Mondays through Friday, 9:00AM to 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

jle
January 29, 2001

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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